REMARKS

Claims 66-83 are pending and under consideration. With this Amendment, pending Claims 66, 69, 70 and 78 are amended and new Claims 84-88 are added. Thus, after entry of this Amendment, Claims 66-88 are pending and under consideration. The amendments to the claims, and the various rejections raised in the Office Action are discussed in more detail, below.

Amendments to the Claims

Claim 66 has been amended to include recite a first scorable homeostatic reporter element comprising at least one scorable reporter gene encoding CD8. Support for the CD8 limitation can be found, for example, in paragraph 125 in the specification as filed and in Example 4. Claim 69 has been amended to recite a second scorable homeostatic reporter element comprising a reporter gene encoding a protein selected from the group consisting of cell surface proteins. Support for the amendment to Claim 69 can be found, for example, in paragraph 125 of the specification. Claim 70 has been amended to recite a proper Markush group. Claim 78 has been amended to clarify that second target element comprises a second selectable marker.

Support for new Claims 84-88 can be found, for example, in paragraphs 71 and 125 in the specification as filed, in Example 4, and in the state of the art existing at the filing date of the application. For example, membrane bound immunoglobulins were known in the art at least by 1988 (see e.g., Molecular Immunology, 3 (B.D. Hames & D. M. Glover eds., IRL Press 1988, attached hereto as Exhibit 1). No new matter is added by virtue of the amendments.

Rejection Under 35 U.S.C. § 112

Claim 5 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite. As Claim 5 was cancelled in the response to final office action mailed August 18, 2006, Applicant assumes that the Patent Office meant to reject Claims 69 and 70 under 35 U.S.C. § 112, second paragraph as being indefinite.

The rejection is moot as applied to amended Claim 69. Claim 70 has been amended to recite a proper Markush group. Applicant respectfully requests that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection Under 35 U.S.C. § 103 (a)

The Patent Office has made the following rejections under 35 U.S.C. § 103(a):

Claims 66 and 70-83 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al.*") in view of Seibler *et al.*, 1997, Biochemistry, 36:1740-1747 ("Seibler *et al.*").

Claims 66 and 70-83 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al.*") in view of Cox *et al.*, U.S. Patent No. 6,140,129 ("Cox *et al.*");

Claims 66-68 and 70-83 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al.*") in view of Seibler *et al.*, 1997, Biochemistry, 36:1740-1747 ("Seibler *et al.*") and Ow U.S. Patent Application Publication No. 2002/0123145; and,

Claims 66 and 69-83 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al.*") in view of Seibler *et al.*, 1997, Biochemistry, 36:1740-1747 ("Seibler *et al.*") and Ogilvy *et al.* 1999, Blood, 94:1855-1863 ("Ogilvy *et al.*").

Applicant traverses the rejections as they apply to amended Claims 66-83 and new Claims 84-88.

A. Criteria for Establishing a Prima Facie Case of Obviousness

Section 103(a) precludes the grant of a patent only if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art

to which the subject matter pertains." 35 U.S.C. § 103(a). The Patent Office bears the initial burden of establishing a case of *prima facie* obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1998); MPEP § 2142.

To establish a proper *prima facie* case, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation that the modification or combination would be successful. Finally, the prior art reference (or references when combined) must teach all the limitations of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), citing *In re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988); MPEP § 2142.

B. The combination of Cheo *et al.* and Seibler *et al.* fails to teach or suggest all of the limitations recited in amended Claims 66 and 70-83

Amended Claims 66 and 70-83 and newly added Claims 84-88 recite a first integration cassette comprising, among other things, an exchangeable reporter segment comprising a scorable homeostatic reporter element, which comprises at least one scorable reporter gene encoding CD8.

As noted by the Patent Office, Cheo *et al.* teach vector compositions comprising selectable markers. The selectable markers taught by Cheo *et al.* include nucleic acid molecules that encode proteins that can be used to select for or against a cell, or that can be used to readily identify a cell, such as phenotypic markers and cell surface markers. The selectable markers of Cheo *et al.* do not teach or describe a scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8.

Seibler *et al.*, teach expression cassettes, comprising a set of FRTs, a reporter and a selectable marker (see, page 1743). The reporter taught by Seibler *et al.*, is luciferase, which is

detected by assaying extracts obtained from lysed cells (see, page 1741). Seibler *et al.* do not teach expression cassettes comprising a scorable homeostatic reporter gene encoding CD8.

At a minimum, the combination of Cheo *et al.* and Seibler *et al.* fails to teach or suggest all of the limitations recited in amended Claims 66 and 70-83 and newly added Claims 84-88. Specifically, the combination of Cheo *et al.* and Seibler *et al.* fails to teach or suggest an integration cassette comprising an exchangeable reporter segment comprising a scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8. Accordingly, the Patent Office has not established a *prima facie* case of obviousness. Applicant respectfully submits that amended Claims 66 and 70-83 and newly added Claims 84-88 are patentable over Cheo *et al.* in view of Seibler *et al.*; thus, a rejection of amended Claims 66 and 70-83 and newly added Claims 84-88 under 35 U.S.C. § 103(a) would be in error.

C. The combination of Cheo *et al.* and Cox *et al.* fails to teach or suggest all of the limitations recited in amended Claims 66 and 70-83

Amended Claims 66 and 70-83 have been summarized above.

The teaching of Cheo *et al.* has been discussed above.

As noted by the Patent Office, Cox *et al.* teach that FLP recombinase activity can be provided in a host cell through the regulated expression of its gene on a plasmid. However, there is no teaching in Cox *et al.* of integration vectors comprising at least one scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8. Thus, the combination of Cheo *et al.* and Cox *et al.* fails to teach or suggest all of the limitations recited in new Claims 66 and 70-83 and newly added Claims 84-88. Specifically, the combination of Cheo *et al.* and Cox *et al.* fails to teach or suggest an integration cassette comprising an exchangeable reporter segment comprising a scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8. Accordingly, the Patent Office has not established a *prima facie* case of obviousness. Applicant respectfully submits that amended Claims 66 and 70-83 and newly

added Claims 84-89 are patentable over Cheo *et al.* in view of Cox *et al.*; thus, a rejection of new Claims 66 and 70-83 and newly added Claims 84-88 under 35 U.S.C. § 103(a) would be in error.

D. The combination of Cheo *et al.*, Seibler *et al.*, and Ow fails to teach or suggest all of the limitations recited in amended Claims 66-68 and 70-83

Amended Claims 66-68 and 70-83 have been summarized above.

The teachings of Cheo *et al.* and Seibler *et al.* have been discussed above.

The Patent Office states that Ow teaches "a first integration cassette (receptor construct) comprising a promoter operably linked to a first exchangeable reporter segment comprising a thymidine kinase (tk) coding region (scorable homeostatic reporter element) and a zeocin resistance coding region (exchangeable reporter gene), wherein the tk coding sequence is linked to a first recombinase recognition site (PP') at its 5' end and to a second recombinase recognition site at its 3'end (PP") (e.g. Figure 4)".

There is no teaching in Ow of integration vectors comprising at least one scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8. Thus, the combination of Cheo *et al.*, Seibler *et al.*, and Ow fails to teach or suggest all of the limitations recited in amended Claims 66-68 and 70-83 and newly added Claims 84-88. Specifically, the combination of Cheo *et al.*, Seibler *et al.*, and Ow fails to teach or suggest an integration cassette comprising an exchangeable reporter segment comprising a scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8. Accordingly, the Patent Office has not established a *prima facie* case of obviousness. Applicant respectfully submits that amended Claims 66-68 and 70-83 and newly added Claims 84-88 are patentable over the combination of Cheo *et al.*, Seibler *et al.*, and Ow; thus, a rejection of amended Claims 66-68 and 70-83 and newly added Claims 84-88 under 35 U.S.C. § 103(a) would be in error.

E. The combination of Cheo *et al.*, Seibler *et al.*, and Ogilvy *et al.* fails to teach or suggest all of the limitations recited in amended Claims 66 and 69-83

Amended Claims 66 and 69-83 have been summarized above.

The teachings of Cheo *et al.* and Seibler *et al.* have been discussed above.

Ogilvy *et al.* teach the use of transgenic vectors for hematopoietic targeting. The vectors taught by Ogilvy *et al.* incorporate CD4 as a mammalian cell surface reporter to facilitate cell by cell analysis. However, there is no teaching in Ogilvy of vectors comprising at least one scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8. Thus, the combination of Cheo *et al.*, Seibler *et al.*, and Ogilvy *et al.* fails to teach or suggest all of the limitations recited in amended Claims 66 and 69-83 and newly added Claims 84-88. Specifically, the combination of Cheo *et al.*, Seibler *et al.*, and Ogilvy *et al.* fails to teach or suggest an integration cassette comprising an exchangeable reporter segment comprising a scorable homeostatic reporter element comprising a scorable reporter gene encoding CD8. Accordingly, the Patent Office has not established a *prima facie* case of obviousness. Applicant respectfully submits that amended Claims 66 and 70-83 and newly added Claims 84-88 are patentable over the combination of Cheo *et al.*, Seibler *et al.*, and Ogilvy *et al.*; thus, a rejection of amended Claims 66 and 70-83 and newly added Claims 84-88 under 35 U.S.C. § 103(a) would be in error.

Conclusion

Amended Claims 66-68 and 70-83 and newly added Claims 84-88 are believed to satisfy all of the criteria for patentability and are in condition for allowance.

No fees beyond those submitted herewith are believed to be due in connection with this Amendment. However, the Commissioner is authorized to charge any additional fees that may be required, or credit any overpayment, to PDL BioPharma, Inc., Deposit Account No. 50-3270 **(Docket No. 118 US UT01)**.

Respectfully submitted,

Date: February 15, 2007

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EXHIBIT 1

MOLECULAR IMMUNOLOGY

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chain C regions mediate immunologic effector functions, such as complement fixation, placental transfer and binding to cell surface Fc receptors that are specific to particular isotypes (9). Functional differences have not been identified for the two isotypes of mammalian L chains, kappa (κ) and lambda (λ). H chain C regions contain between two and four domains (CH_1, CH_2 and CH_3 in *Figure 1*) that are distantly homologous to each other and each L chain C region domain (CL; *Figure 1*). Certain H chain isotypes also contain a hinge region (Figure 1) that may facilitate antigen binding by increasing H chain flexibility (10). H chains can be produced in either a membrane-bound or a secreted form (e.g. μ_m or μ_s for μ H chains), which are distinguished by specific sequences at their carboxy-termini (11–13). A membrane-bound Ig molecule is monomeric, but secreted Ig molecules are composed of between one and five monomers, depending upon their class (4).

2.2 Antibody production is triggered by clonal selection

Each B lymphocyte displays on its surface a unique species of membrane-bound Ig that functions as an antigen receptor. The clonal selection theory (*Figure 2*) states that the immune response to an antigen is initiated when that antigen is recognized by a B lymphocyte surface receptor of a pre-existing specificity (14). When a particular B lymphocyte binds antigen, it is induced to proliferate. B lymphocytes within this selected clone can differentiate into plasma cells, which produce large amounts of the selected Ig molecule in secreted form as antibody. This mechanism requires that each Ig molecule produced by a given B lymphocyte display an identical set of antigen-binding specificities. Otherwise, antigenic triggering of a B lymphocyte clone might lead to production of multiple different and potentially harmful antibodies (e.g. autoreactive), and production of the selected antibody might be inefficient. Each B lymphocyte produces Ig molecules with identical antigen-binding specificities because it expresses as Ig the products of only a single H and a single L chain gene, a phenomenon referred to as allelic exclusion (15,16). As is discussed in detail in Section 8, Ig gene assembly appears to be regulated specifically to impose H and L chain allelic exclusion (17).

3. Model systems for studying B cell differentiation

In mammals, B lymphocytes are generated in the liver during fetal life, but shortly after birth the bone marrow becomes the site of lymphopoiesis and remains so throughout adult life (18). In the bone marrow, B lymphocytes arise from a small self-renewing population of stem cells. These lie within a matrix of stromal cells that produce factors which immature B lymphocytes require for growth. Ig genes are assembled during this differentiation process, which generates 'virgin' B lymphocytes

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